

Anti-Thrombotics In Stroke

when to start and when to stop

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No Relevant Disclosures

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He has afib but was discharged only on aspirin – when should I restart his anticoagulation ?

This person was discharged 1 week ago with a subdural. Should they be back on aspirin?

My patient is currently on warfarin but wants to get pregnant. Is that safe?

Common questions that arise post-Stroke

The report says “likely amyloid angiopathy” – what do I do about their antithrombotics?

Why is everyone talking about putting TIA patients on BOTH aspirin and plavix for a few weeks?



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Outline

- **Physiology** – types of clots and the logic behind the different choices for antithrombotic therapy
- **Timing:** When should antithrombotics be started...
 - after an **ischemic stroke**?
 - after a **hemorrhagic stroke**?
- **Safety:** What to consider in selecting antithrombotic therapy
 - in **pregnancy**
 - in patients with **cerebral amyloid angiopathy**
- **DAPT:** When is **duo-antiplatelet treatment** indicated?

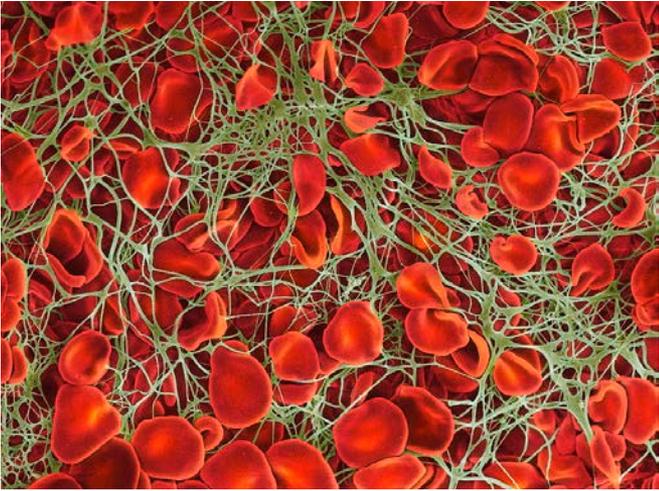


Physiology of Clots

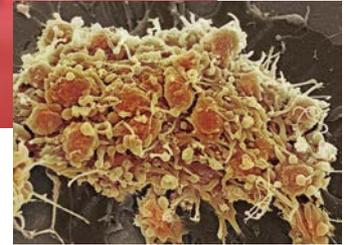
thrombosis - an **obstruction of blood flow** due to a **localized occlusive process** within one more more blood vessels.

Physiology of Clots

RED THROMBI



WHITE THROMBI

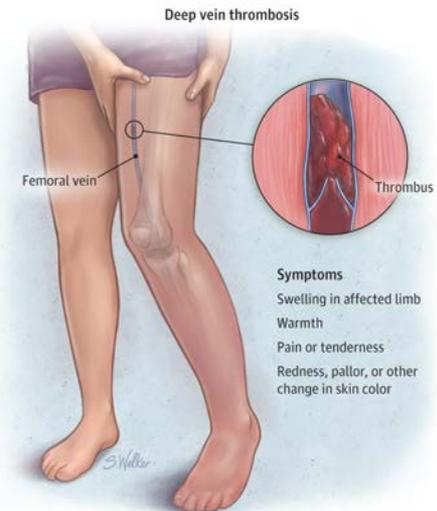
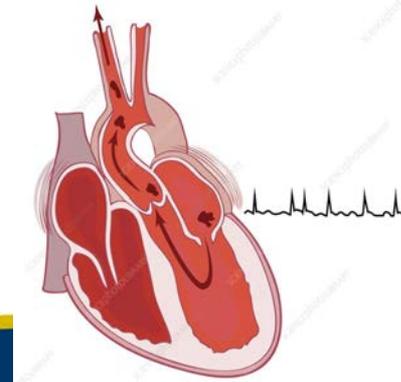
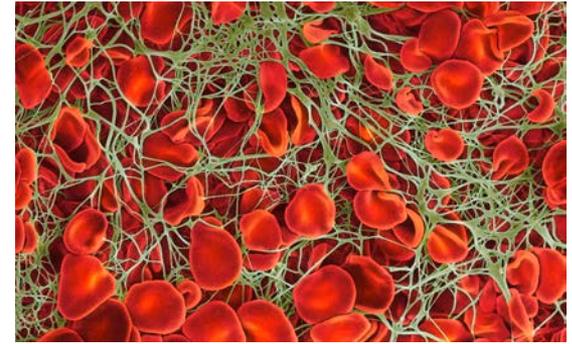


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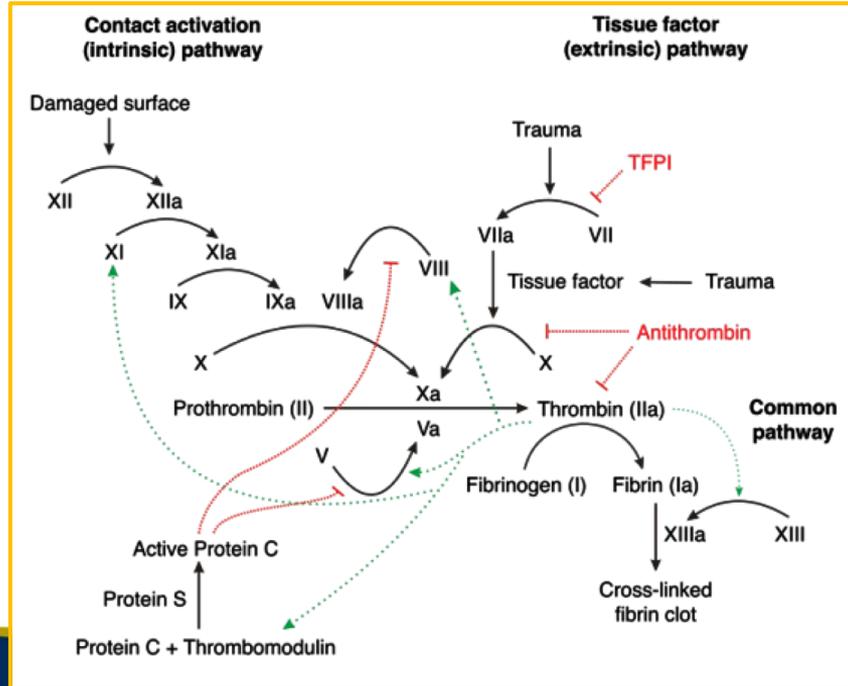
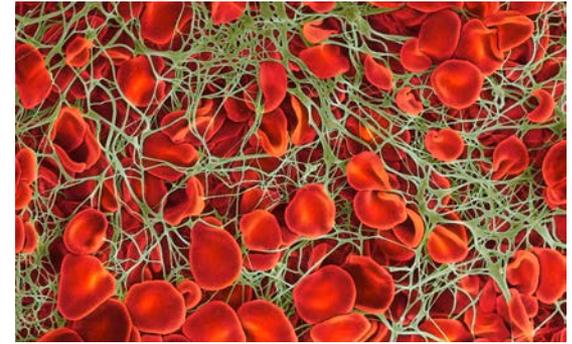
RED THROMBI

- **Erythrocytes + Fibrin**
- tend to develop in **low flow situations**:
 - dilated cardiac atria / afib
 - regions of ventricular hypokinesia (ventricular aneurysms, low EF, or MI)
 - leg/pelvic veins (paradoxical emboli)
 - Cerebral Sinus Venous Thrombosis (CSVT) (increased risk with Hypercoagulable Disorders)



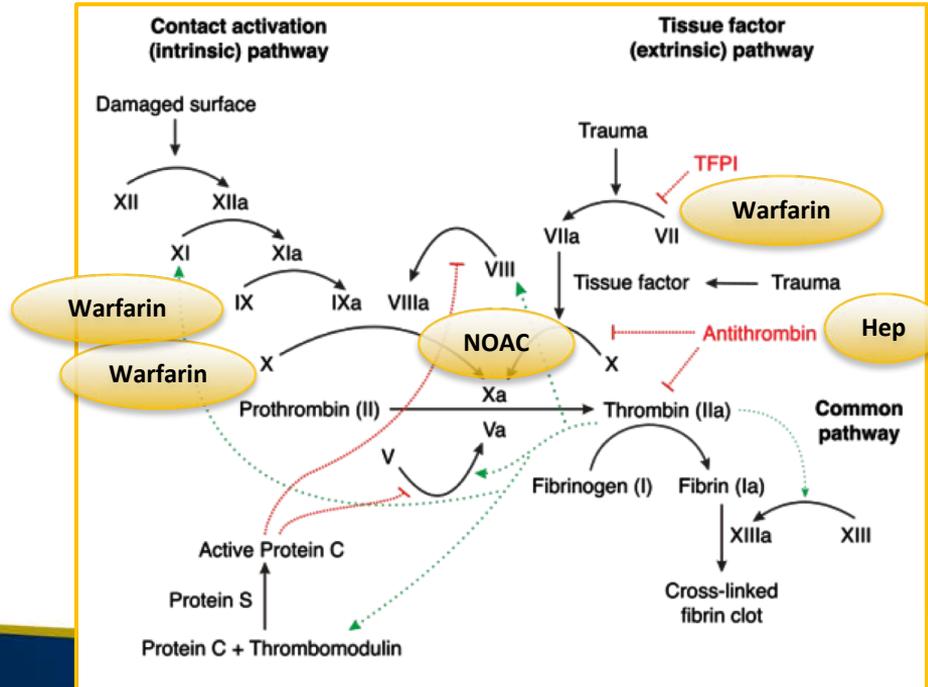
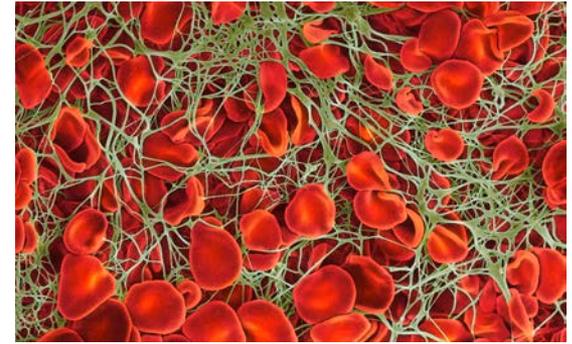
RED THROMBI

- Erythrocytes + Fibrin
- formed by activation of circulating coagulation factors



RED THROMBI

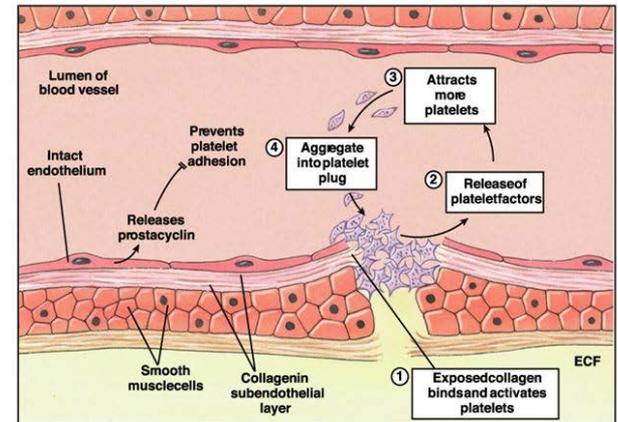
- Erythrocytes + Fibrin
- formed by activation of circulating coagulation factors



Treated by
AntiCoagulants:
Heparin / LMWH
Warfarin
NOACs (= "DOACs", ie
apixaban, dabigatran,
edoxaban, rivaroxaban)

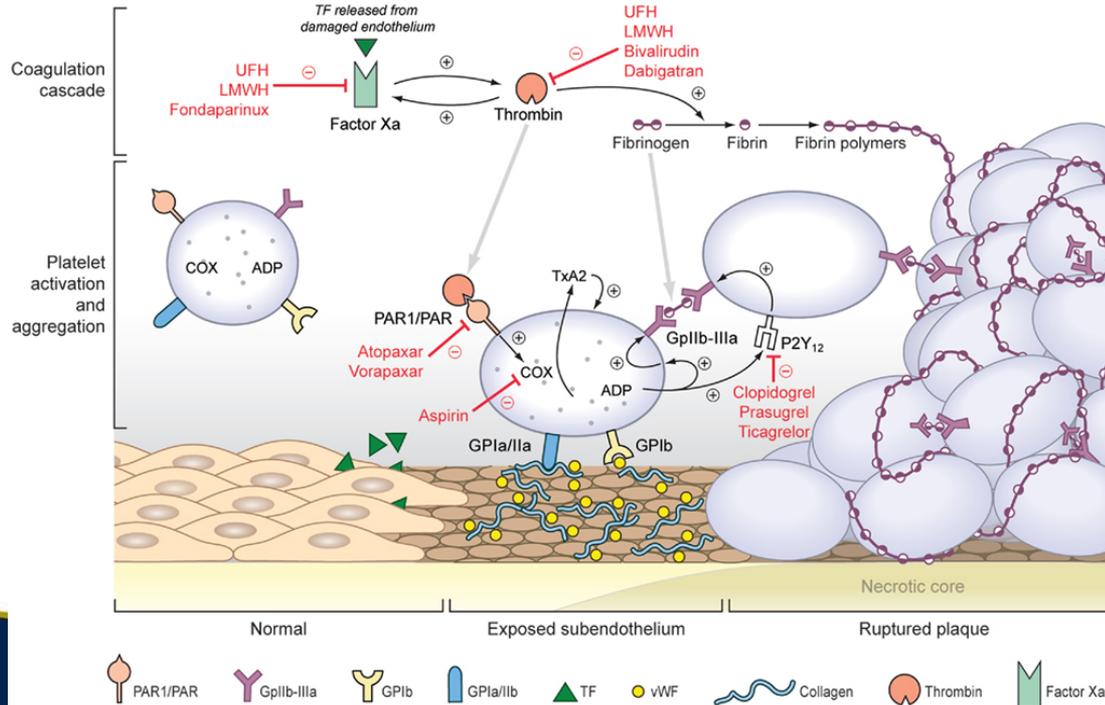
WHITE THROMBI

- **Platelets + Fibrin**
- Form in **fast-moving bloodstreams**
- In areas of **abnormal/irregular endothelial surface** :
 - platelets adhere to areas of denuded, rough or abnormal endothelium / valves
 - platelets aggregate → white clot
 - platelet activation → stimulates thrombin generation
 - red thrombi can grow superimposed on white thrombi (so actual thrombus causing stroke may be mixed white and red clot)



WHITE THROMBI

- **Platelets + Fibrin**
- Platelet activation leads to platelet aggregation, activation of other platelets and fibrin binding:



Treated by

AntiPlatelets:

COX inhibitor: **Aspirin**

PDIII Inhibitors

Cilostazol

Dipyridamole (Aggrenox)

P2Y12 Inhibitors:

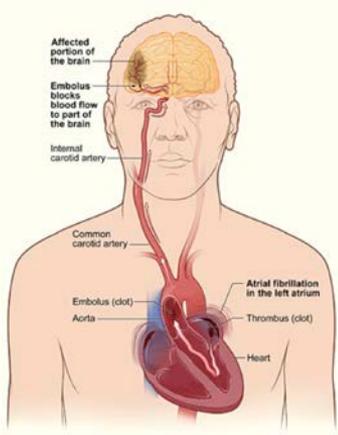
Clopidogrel (Plavix)

Ticagrelor (Brilinta)

Physiology of Clots

RED THROMBI

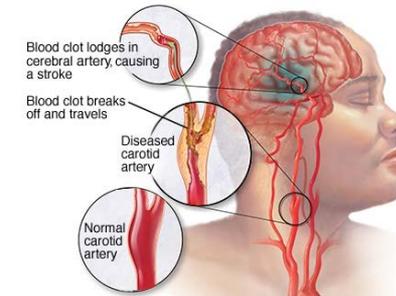
Cardioembolism
DVTs
Hypercoagulable disorders



**Treated by
AntiCoagulation**

WHITE THROMBI

Thromboembolism
Lacunar infarcts



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**Treated by
AntiPlatelets**

+ CV Risk factor modification, removal of causes of secondary hypercoag/erythremia such as cigarette smoking, etc

But some decisions are still tricky...



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But some decisions are still tricky...

(1) Timing:

- when to start antithrombotics after an ischemic stroke?
- when/if to restart antithrombotics after a hemorrhagic stroke?

(2) Special cases:

- what to do with patients thought to have Cerebral Amyloid Angiopathy?
- what antithrombotics can be used in Pregnancy?

(3) The buzz about DAPT:

- when should we be using DAPT vs monotherapy?

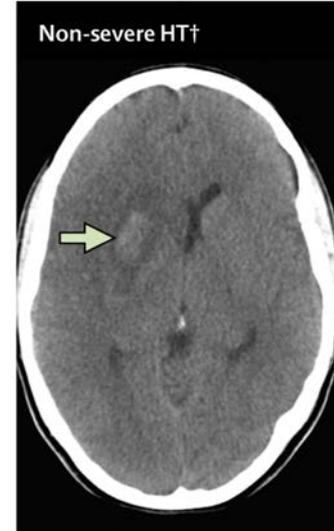


When to start AC after Ischemic Stroke?

- **Common problem** – 13-26% of iStrokes due to afib
- **High clinical uncertainty** – 95% of UK stroke physicians reported uncertainty as to ideal timing
- **Need to balance:**
 - Risk of **recurrent ischemic stroke** (0.5 -1.3% daily risk in first 14d)
 - Risk of **hemorrhagic transformation**

When to start AC after Ischemic Stroke?

- Hemorrhagic transformation is not that rare
 - Up to 9% (petechial)
 - Severe IPH less common (3%) and associated with:
 - larger ischemic stroke size
 - acute recanalization therapies
 - Risk *suspected* to be increased with AC – but *no data*



When to start AC after Ischemic Stroke?

Given paucity of evidence, guidelines are varied (and based expert opinion):



AHA: start oral anticoagulant **4-14d** after onset of neurological sx



EUROPEAN
SOCIETY OF
CARDIOLOGY

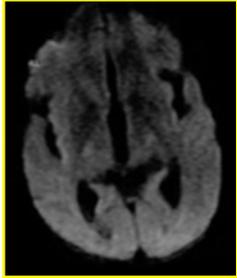
European Heart Rhythm Association / European Society of Cardiology (EHRA-ESC): "**1-3-6-12 rule**"



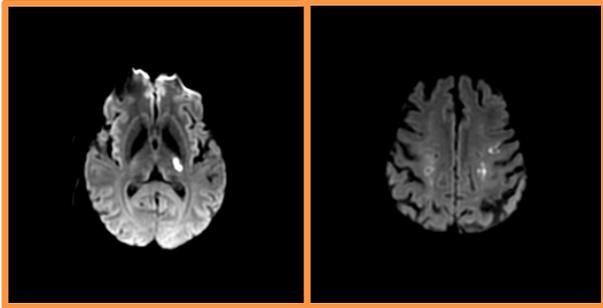
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When to start AC after Ischemic Stroke?

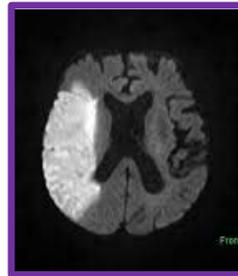
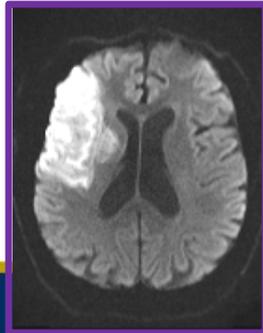
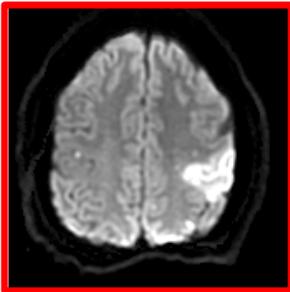


TIA



Small

Moderate



Large

The “1-3-6-12” rule

Event	# of days before starting AC
TIA	1
Small, non-disabling infarct	3
Moderate infarct	6
Large infarct involving large area of arterial territory	12

When to start AC after Ischemic Stroke?

Given paucity of evidence, guidelines are varied (and based expert opinion):



AHA: start oral anticoagulant **4-14d** after onset of neurological sx



European Heart Rhythm Association / European Society of Cardiology (EHRA-ESC): "**1-3-6-12 rule**"

But ...no guidelines distinguish between warfarin and NOACs

The "1-3-6-12" rule

Event	# of days before starting AC
TIA	1
Small, non-disabling infarct	3
Moderate infarct	6
Large infarct involving large area of arterial territory	12

When to start AC after Ischemic Stroke?

So what about NOACs? Things to consider:

- Current guidelines - based on data from hep, LMWH or warfarin
- The NOACs have approximately 1/2 the risk of ICH in general (as compared to warfarin) - but none of the initial trials included patients with recent ischemic stroke
- Preliminary NOAC studies suggest that starting 3-5d post ischemic stroke has a low frequency of symptomatic ICH, while starting later (>7 or >14d) has increased frequency of recurrent ischemic stroke (*prospective observational studies, 2 small RCTs*)

When to start AC after Ischemic Stroke?

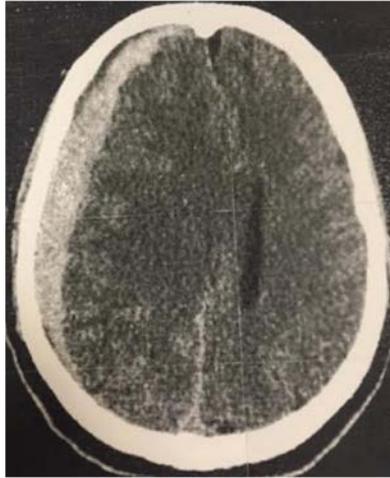
So what about NOACs? Things to consider:



- Currently 4 RCTs actively enrolling comparing earlier versus later NOAC initiation post ischemic stroke
- ~9000 patients → should have adequate numbers/power to confirm prior preliminary results

(Results expected in 2021)

Timing: Post Hemorrhagic Stroke



Timing: Post Hemorrhagic Stroke

Again, data is limited.



AHA ICH Guidelines (2015): The optimal timing to resume oral anticoagulation after anticoagulant-related ICH is **uncertain**. Avoidance of oral anticoagulation for **at least 4 weeks**, in patients without mechanical heart valves, might decrease the risk of ICH recurrence (*Class IIb; Level of Evidence B*). (New recommendation) If indicated, **aspirin monotherapy can probably be restarted in the days after ICH**, although the optimal timing is uncertain (*Class IIa; Level of Evidence B*). (New recommendation) (whether NOAC uses decreases risk is uncertain)



(No guidelines from ESC)

Timing: Post Hemorrhagic Stroke

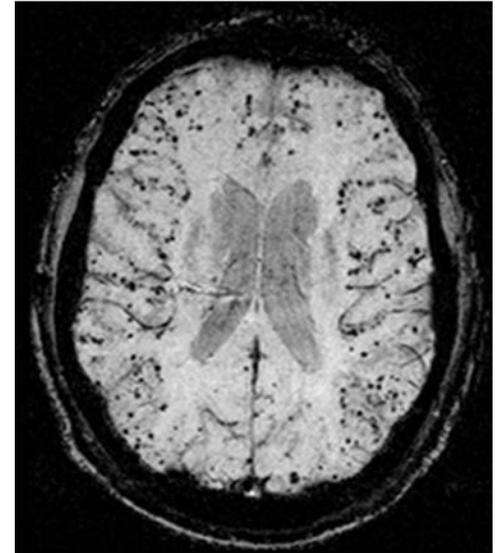
A reasonable strategy:

- Wait **2 weeks** prior to restarting **antiplatelet** therapy
- Wait **4 weeks** prior to restarting **anticoagulation**
- Obtain non-contrast CT to confirm no fresh bleeding prior to restarting antithrombotics

(and always re-consider AC risk/benefits prior to restarting)

Cerebral Amyloid Angiopathy (CAA)

- **Cerebral small vessel disease**
- **Amyloid-beta peptide** deposits in the small to medium-sized blood vessels (brain/leptomeninges)
- **increasing frequency with age** (~2% of 65-75yo, ~12% in >85yo)
- Important cause of primary **lobar hemorrhage** (37-74% of non-traumatic ICH) and **cognitive impairment**
- **Cerebral microhemorrhages (CMBs)** seen on MRI due to vessel leakage --> perivascular hemosiderin deposits

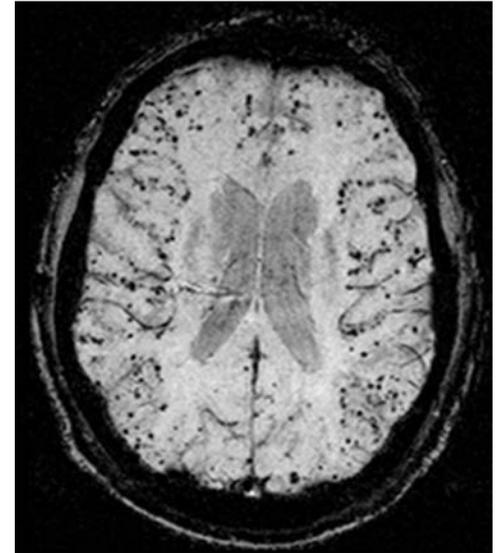


Cerebral Amyloid Angiopathy (CAA)

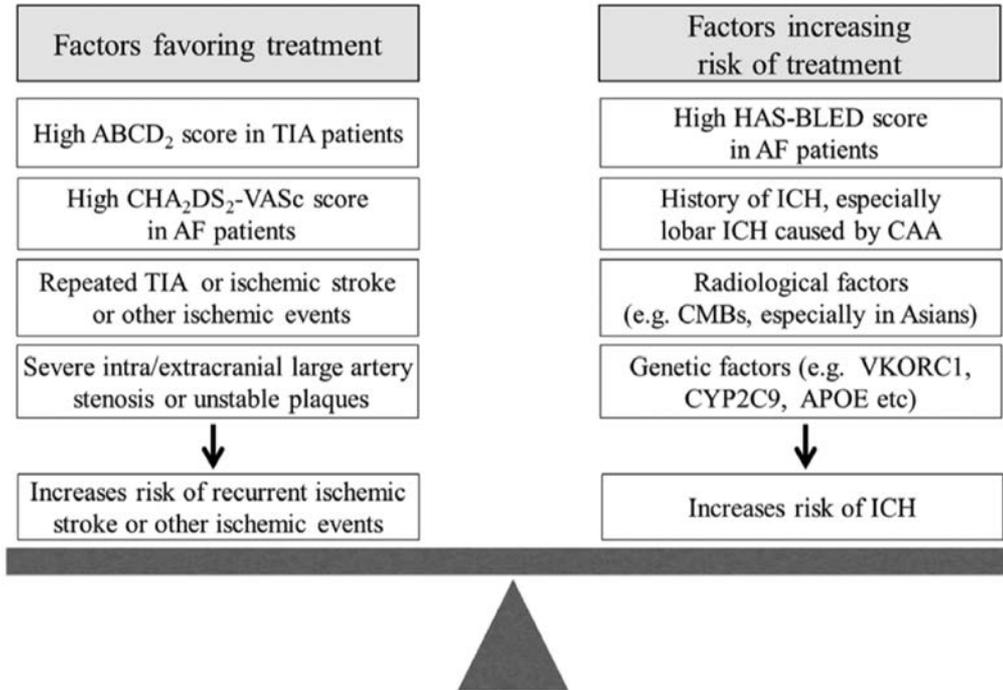
Given that both CAA and afib incidence increases with age, not uncommon to have patient with both

→ **How should patient with both afib and CAA be managed?**

- Warfarin increases risk of ICH in patients with CAA by 7-10 fold
- Antiplatelets increase risk of ICH as well, but less than warfarin (4 fold after prior ICH)
 - ultimately need to balance risk/benefits



Cerebral Amyloid Angiopathy (CAA)



- Patients with prior ICH and CAA are much more likely to have recurrent bleeds
- Increased number of CMBs is associated with increased risk of ICH (5x increase if <4 CMBs, 14x increase if ≥ 5 CMBs)

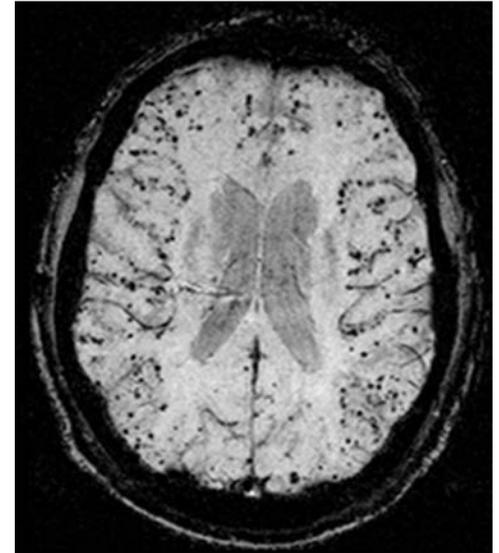
Cerebral Amyloid Angiopathy (CAA)

Given that both CAA and afib incidence increases with age, not uncommon to have patient with both

→ **How should patient with both afib and CAA be managed?**

No easy answer. Recommend:

- *Frank risk/benefit discussion with family*
- *Assessment of ischemic stroke risk vs hemorrhagic stroke risk*
- *Would avoid anticoagulation if confident of diagnosis*
- *Probably appropriate to use aspirin unless history of prior ICH or CMBs ≥ 5*



Cerebral Amyloid Angiopathy (CAA)

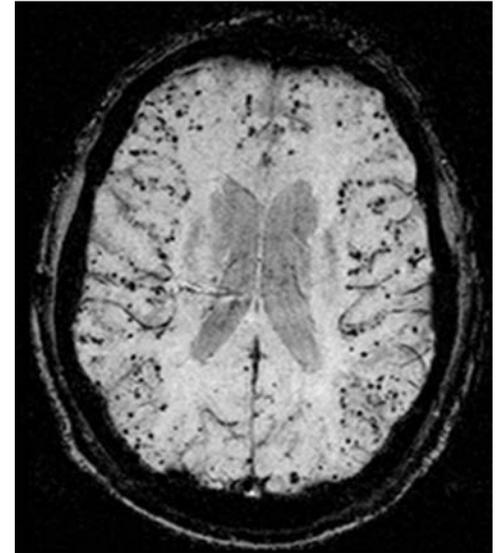
Given that both CAA and afib incidence increases with age, not uncommon to have patient with both

→ **How should patient with both afib and CAA be managed?**



Future Considerations:

- *Use of Watchman device for these patients*
- *Use of NOACs (lower ICH rates in original studies, and several small studies suggest NOAC use does not increase rate of CMB formation (AVERROES, NAVIGATE-ESUS sub-analysis))*



Anti-Thrombotics in Pregnancy

Pathophysiology of Stroke in Pregnancy:

(1) Effect of pregnancy on vascular & connective tissues:

- walls of arteries modified during pregnancy to help create hemodynamic changes in pregnancy - reduction in collagen and elastin

(2) Effect of pregnancy on coagulability

- changes in relative amounts of coagulation factors

→ increased risks of vascular events



Anti-Thrombotics in Pregnancy

Heparin gtt and LMWH

– considered SAFE in Pregnancy

- do NOT cross placenta
- dose needs to be adjusted in pregnancy
(due to increased blood volume and upregulated enzymes → shorter half life)



Anti-Thrombotics in Pregnancy

Warfarin

– considered NOT SAFE in Pregnancy

- Teratogenic
- “Fetal Warfarin Syndrome” (low birthweight, slow growth, mental retardation, deafness, malformed bones/cartilage/joints)



Anti-Thrombotics in Pregnancy

NOACs

– AVOID in Pregnancy/Lactation

- Insufficient data at this time
- BUT, studies suggest NOACs cross placenta, and detectable levels in human milk



Anti-Thrombotics in Pregnancy

Aspirin

– considered SAFE in Pregnancy

- Usual recommendation is 81mg
- Start at 12-16 weeks*

*increased risk of hemorrhage/miscarriage but NOT increased risk of fetal anomaly (so if needed could continue throughout pregnancy).



Anti-Thrombotics in Pregnancy

Aspirin

- cautiously ok in lactation
- UpToDate says **81mg can be used** “for vascular indications”
- (but known to cross into breast milk – could cause hemorrhagic complications or Reye’s at high doses)



Anti-Thrombotics in Pregnancy

other antiplatelets

- **AVOID** in Pregnancy/Lactation
- limited data on clopidogrel, ticagrelor (case reports) so **NOT** recommended over aspirin



DAPT: indications and timing

Duo-AntiPlatelet Therapy (DAPT)



Cerebrovascular Indications*:

1. Symptomatic Intracranial Stenosis
2. High Risk TIA or Minor Stroke

**other indications include recent stenting, etc*

DAPT: indications and timing

1. Symptomatic Intracranial Stenosis – **3 MONTHS**

SAMMPRIS trial (2011)

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

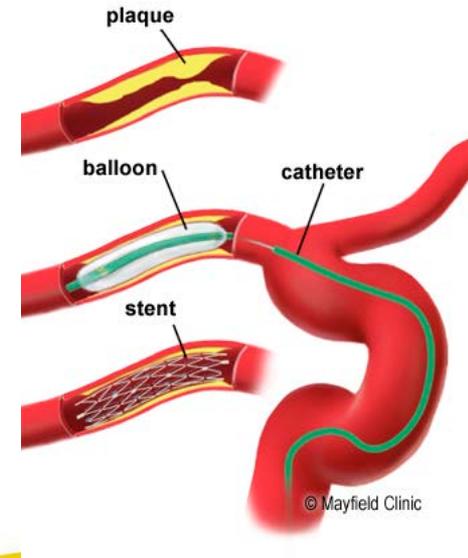
Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Colin P. Derdeyn, M.D.,
Tanya N. Turan, M.D., David Fiorella, M.D., Ph.D., Bethany F. Lane, R.N.,
L. Scott Janis, Ph.D., Helmi L. Lutsep, M.D., Stanley L. Barnwell, M.D., Ph.D.,
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Michel T. Torbey, M.D., M.P.H., Osama O. Zaidat, M.D.,
Zoran Rumboldt, M.D., and Harry J. Cloft, M.D., Ph.D.,
for the SAMMPRIS Trial Investigators*

DAPT: indications and timing

1. Symptomatic Intracranial Stenosis – **3 MONTHS**

SAMMPRIS trial (2011)

- Patients with recent TIA/CVA due to 70-99% intracranial artery stenosis
- Randomized to Aggressive Medical Therapy [325 ASA + Plavix and aggressive Risk Factor Mgmt]. +/- angioplasty/stenting

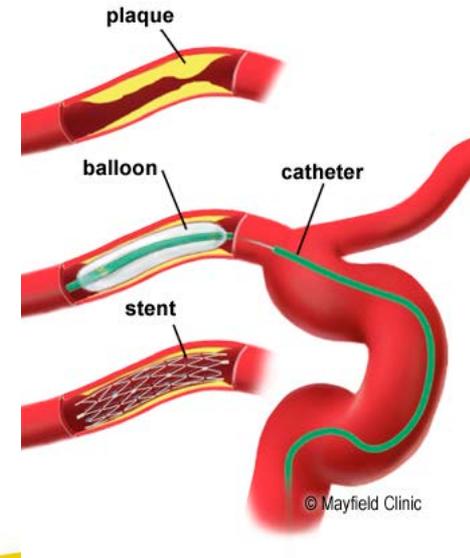


DAPT: indications and timing

1. Symptomatic Intracranial Stenosis – **3 MONTHS**

SAMMPRIS trial (2011)

- Stopped early because stenting group had significantly higher rates of stroke/death (14.7 vs 5.8% in 30d)
- *Aggressive Med Mgmt also better than prior studies that showed 10.7% 30d stroke/death rate*
- Suggests that **3 months DAPT beneficial after TIA/stroke due to severe intracranial stenosis**



DAPT: indications and timing

Duo-AntiPlatelet Therapy (DAPT)



Cerebrovascular Indications*:

1. Symptomatic Intracranial Stenosis
2. High Risk TIA or Minor Stroke

**other indications include recent stenting, etc*

DAPT: indications and timing

2. High Risk TIA / Minor Stroke – **10 – 21 DAYS**

POINT trial (2018)



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Johnston et al, NEJM 2018.

DAPT: indications and timing

2. High Risk TIA / Minor Stroke – 10 – 21 DAYS

POINT trial (2018)

BACKGROUND:

Patients with high-risk TIA or minor stroke have INCREASED risk of recurrent stroke/death

ABCD2 Score (TIA)

- *Age*—1 point if ≥ 60 years
- *Blood pressure*—1 point if $\geq 140/90$ mm Hg
- *Clinically*—1 point if speech disturbance only, 2 points if unilateral weakness
- *Duration*—1 point if 10 minutes to 1 hour, 2 points if ≥ 1 hour
- *Diabetes*—1 point if present

ABCD2 score	7 day Stroke Risk
-------------	-------------------

1-3	1.2%
-----	------

4-5	5.9%
-----	------

6-7	11.7%
-----	-------

Minor stroke

- Severity defined as NIHSS score ≤ 3



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DAPT: indications and timing

2. High Risk TIA / Minor Stroke – **10 – 21 DAYS**

POINT trial (2018)

4,881 Patient with High-Risk TIA (ABCD2 score ≥ 4)
or Minor Stroke (NIHSS ≤ 3)

Randomized to Monotherapy (Aspirin (50-325mg/d)+ Placebo) vs DAPT (Aspirin + Clopidogrel (600mg loading dose then 75mg/d))

→ Lower rates of ischemic stroke, MI, death at 90d in DAPT group (5% vs 6.5%)

But increased rates of major and minor hemorrhage, death from any cause in DAPT group (0.9% vs 0.4% of major hemorrhage)

DAPT: indications and timing

2. High Risk TIA / Minor Stroke – 10 – 21 DAYS

Prasad et al BMJ 2018: recent review, cumulative data from 3 RCTs of DAPT vs aspirin alone

Comparison of benefits and harms

Favours dual antiplatelets

No important difference

Favours single agent

Within 90 days

Events per 1000 people

Evidence quality

Outcome	44	19 fewer	63	Evidence quality
Non-fatal recurrent stroke	44	19 fewer	63	★★★★ High
All cause mortality	6	No important difference	5	★★★★ Moderate
Functional disability	128	14 fewer	142	★★★★ Moderate
Poor quality of life	55	13 fewer	68	★★★★ Moderate
Recurrent TIA	36	No important difference	40	★★★★ Moderate
Moderate or major bleeding	5	2 fewer	3	★★★★ Moderate
Minor bleeding	13	7 fewer	6	★★★★ High

Combined Trials:

FASTER:

396 pts, North America

CHANCE:

5170 pts, China

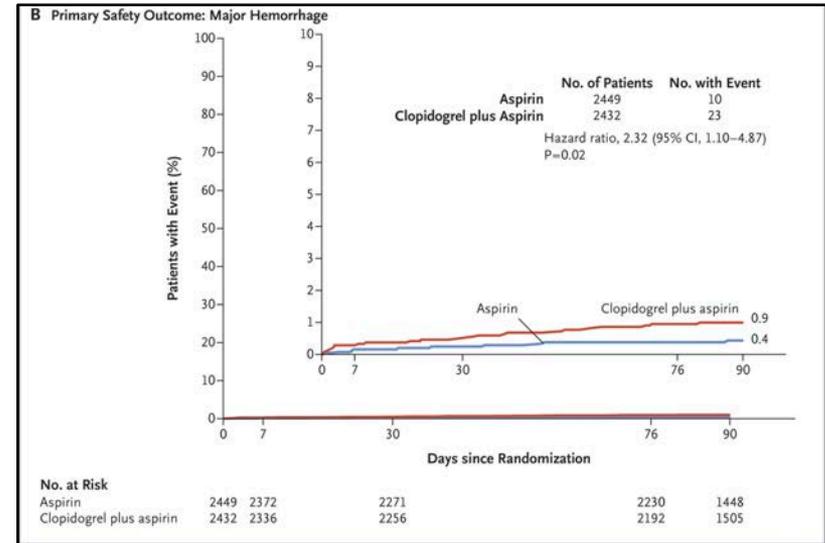
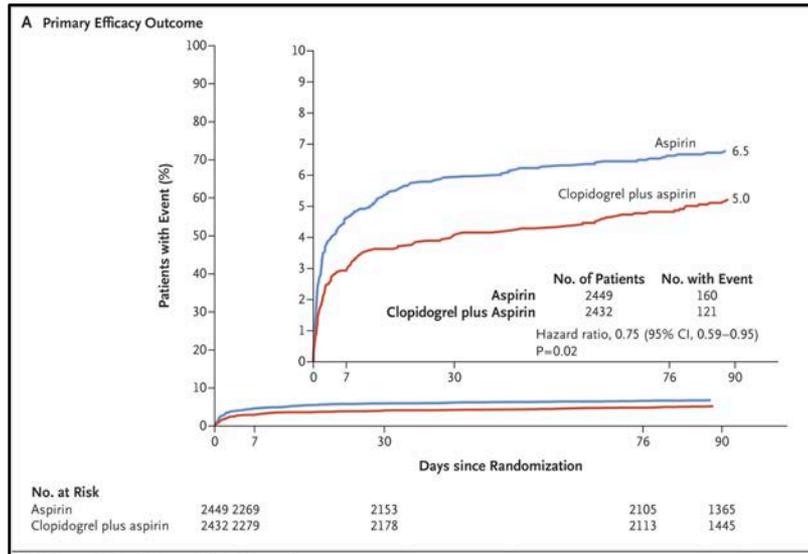
POINT:

4881 patients, 10 countries

→ total of **10,447 patients**

DAPT: indications and timing

2. High Risk TIA / Minor Stroke – 10 – 21 DAYS



DAPT: indications and timing

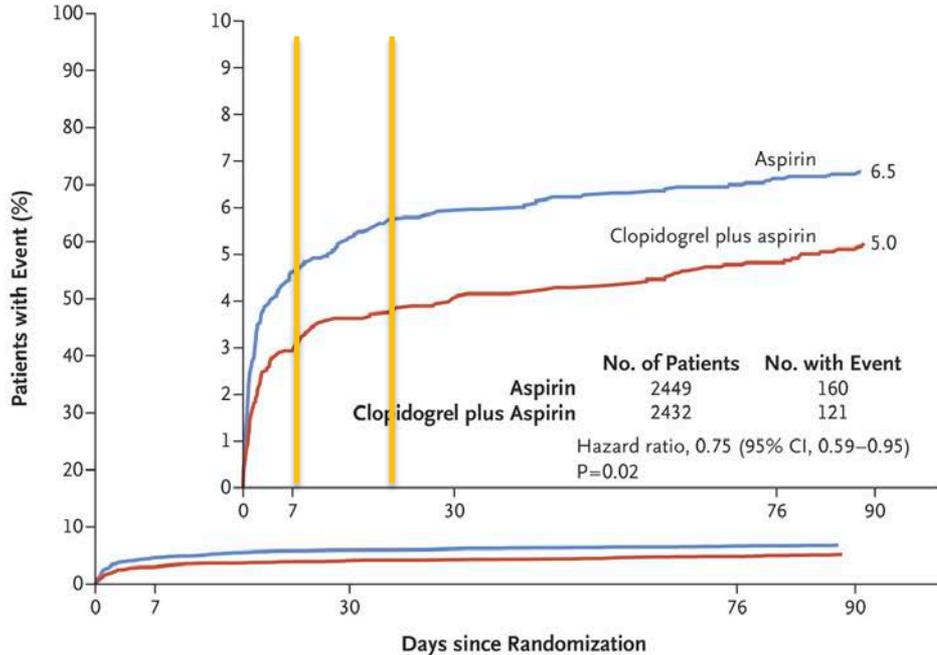
2. High Risk TIA / Minor Stroke – 10 – 21 DAYS

POINT trial:

90% of “efficacy events” occurred in first 30d (and majority in first 7d)

→ Reasonable to prescribe 10-21d of DAPT after high risk TIA or minor stroke

A Primary Efficacy Outcome



DAPT: indications and timing

Duo-AntiPlatelet Therapy (DAPT)



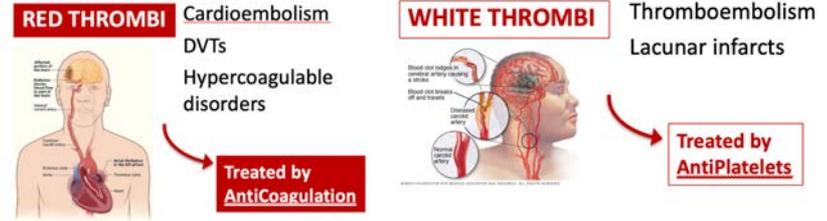
Cerebrovascular Indications*:

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**other indications include recent stenting, etc*

Summary/Take-Home Points

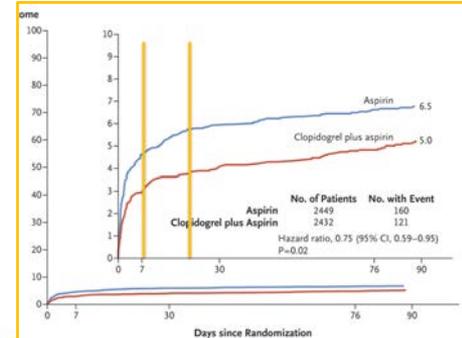
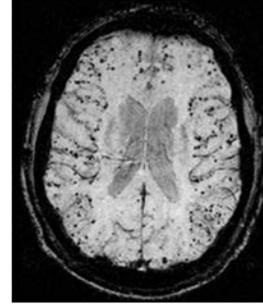
1. Choice of antiplt vs AC depends on presumed mechanism of stroke
2. **After ischemic stroke:** Consider waiting **1,3,6, or 12 days** depending on size of infarct, prior to starting AC
3. **After ICH:** recommend waiting **2 weeks prior to starting antiplatelets, 4 weeks prior to starting AC**, and consider obtaining a **CT scan prior** to starting therapy



The "1-3-6-12" rule	
Event	# of days before starting AC
TIA	1
Small, non-disabling infarct	3
Moderate infarct	6
Large infarct involving large area of arterial territory	12

Summary/Take-Home Points

4. Be **cautious** in giving antithrombotics in patients with **multiple lobar micro bleeds** (because of concern for CAA and risk of ICH)
5. In **pregnancy**, switch to **LMWH** for anticoagulation (not warfarin or NOACs), and use **aspirin** for antiplatelet treatment
6. Consider starting all patients with **high risk TIA or small strokes on DAPT for 10-21d...**
...but watch out for patients who have accidentally been left on DAPT indefinitely



Anti-Thrombotics In Stroke

when to start and when to stop

Ania Busza MD PhD

Assistant Professor of Neurology

University of Rochester School of Medicine and Dentistry



Questions?



Extra slides

Can you give tPA in Pregnancy?

Officially - tPA is category C (no well-controlled studies)

Theoretical risks to consider:

- Maternal/placental hemorrhage
- Placental abruption
- Fetal loss
- Preterm delivery

—> but these are all THEORETICAL and not shown to be increased in studies

one lit review - looking at multiple case studies:

Total 24 pts who were given tPA when pregnant:

1 death

1 intrauterine hematoma and termination of pregnancy (12 weeks gestation)

1 lost pregnancy - but decreased movements had already been noted in that baby

Neuro improvement occurred in 88%, Neuro complication 4%

==> Data is VERY limited, but current review of lit suggests that tPA in pregnancy is relatively safe.



